Proposed Project: Influence of Route of Nicotine Administration, Species, and Age on Nicotine Pharmacokinetics in Mice and Rats

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1. Present Research Related to Nicotine

During the last three years our laboratories have been funded by The Council for Tobacco Research to characterize in vivo nicotine metabolism in the laboratory mouse. The initiation of these studies, however, was dependent upon the development of specific and sensitive analytical methods to quantitate nicotine and its metabolites in extracts of mouse tissue. To date, analytical techniques have been developed to measure nicotine, cotinine, and nicotine N-oxide. These analytical techniques have allowed us to establish the pharmacokinetic profiles of nicotine and cotinine in blood, brain, and liver of male mice from three inbred mouse strains (C57, DBA, and C3H) given a 1.0 mg/kg intraperitoneal dose of nicotine. Our results indicate that the half-life of nicotine (6 - 9 min) and cotinine (25 min) is similar in the three inbred strains. Nicotine N-oxide half-life measured in the liver of these inbred strains, after a 1.0 mg/kg nicotine dose, ranges from 13 - 27 min. Nicotine half-life in DBA, C57, and C3H female mice given a 1.0 mg/kg i.p. nicotine dose is slightly shorter (4 - 5 min) when compared to that observed in male mice. We have also investigated the effects of chronic cigarette smoke exposure on nicotine pharmacokinetics in male mice of the aforementioned inbred strains. Nine days of chronic cigarette smoke, administered by the Walton horizontal smoking machine, increases nicotine half-life 53% in C3H mice while nicotine half-life is decreased 20 - 30% in DBA and C57 mice. In summary, the studies we have conducted suggest that such factors as genotype, gender, and chronic cigarette smoke exposure influence nicotine pharmacokinetics.

2. Plans and Goals

a) Influence of Route of Nicotine Administration on Nicotine Pharmacokinetics

While these data suggest that nicotine metabolism and disposition may be influenced by several factors, it should be considered that the pharmacokinetic profiles established in our studies are based on the intraperitoneal route of nicotine administration. Thus, we propose to reassess these profiles following intravenous nicotine administration as well as the natural route of nicotine exposure via inhalation of cigarette smoke. The latter route of administration circumvents the first-pass effect of hepatic nicotine metabolism which is observed following administration by the intraperitoneal or intravenous routes. Thus, we would predict that nicotine administration via inhalation would result in the most meaningful nicotine pharmacokinetics profile.

Source: https://www.industrydocuments.ucsf.edu/docs/zryb0000

b) Species Comparison of Nicotine Metabolism

A limited number of investigators have studied nicotine pharmacokinetics in the rat. Since our nicotine pharmacokinetic data in the mouse suggest that there may be a large species difference, we are proposing to establish nicotine and cotinine pharmacokinetic profiles in the rat. To be consistent with the studies proposed in 2a, nicotine would be administered by the intravenous route and inhalation of cigarette smoke.

c) Influence of Age and Prenatal Exposure to Nicotine on Nicotine Metabolism and Disposition

Initially, the laboratory mouse would be used as the animal model for these studies. Nicotine pharmacokinetics would be evaluated in inbred mice at the age of 20, 40, 60, 120, 200, and 365 days. Nicotine would be administered intravenously or through cigarette smoke. Data from these studies will serve as baseline information for experiments designed to study the influence of exposure to cigarette smoke in utero on the developmental pattern of nicotine metabolism in the mouse between 20 and 120 days of age. In utero exposure to cigarette smoke would be initiated during the second or third trimester of pregnancy (days 7 - 14 and 15 - 21, respectively). These studies could be expanded to include three inbred strains if warranted.

3. Anticipated Duration of Time

The analytical methods necessary to measure nicotine and its metabolites are routinely used in our laboratories and would not need further refinement or validation for the proposed studies. As a result, we anticipate that the studies cited in sections 2a, 2b, and 2c could be completed in two years.

4. Estimated Cost

a.	Personnel	
	1 full-time postdoctoral Research Associate	$17,000
	Hourly assistance (Animal care and maintenance)	2,500
	1 month of summer salary and benefits for P.I. and Co-Investigator	7,500
b.	Supplies and Chemicals: solvents, glassware, consumables, chromatographic columns, etc.	5,000
c.	Equipment maintenance and consumables for operation of instruments	3,500
d.	Animals	1,500
e.	Miscellaneous: xeroxing, publication costs, travel, telephone, postage, etc.	2,000
	Total estimated budget (first year)	$39,000

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